

Application No. 10/038,591

Filed: January 4, 2002

Title: ANTIBODIES TO INSULIN-LIKE GROWTH FACTOR I RECEPTOR

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1-19. (Cancelled)

20. (Cancelled)

21-22. (Cancelled)

23. (Currently amended) A method of detecting the presence or location of an IGF-IR-expressing tumor in a subject in need thereof, comprising the steps of:

a) administering the antibody or antigen-binding portion according to claim 34 ~~or an antibody according to claim 39 or 46~~ to the subject; and

b) detecting binding of said antibody,

wherein said binding indicates the presence or location of the tumor.

24. (Currently amended) A method of treating cancer in a human patient wherein said patient overexpresses IGF-I or IGF-IR, comprising the step of administering to the human patient an amount of the antibody or antigen-binding portion according to claim 34 effective to treat said cancer.

25. (Currently amended) A method of treating a patient in need thereof, wherein said patient overexpresses IGF-I or IGF-IR, with the antibody or antigen-binding portion thereof according to claim 34, comprising the step of administering to the patient an effective amount of the antibody.

26. (Currently amended) The method according to ~~either of claims claim~~ 24 ~~or 25~~, further comprising the step of administering an anti-neoplastic, anti-tumor, anti-angiogenic or chemotherapeutic agent.

27. (Cancelled)

28. (Cancelled)

29. (Cancelled)

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30. (Cancelled)

31. (Cancelled)

32. (Cancelled)

33. (Cancelled)

34. (Currently amended) A ~~human~~ monoclonal antibody that specifically binds ~~human~~ insulin-like growth factor I receptor (IGF-IR) or an antigen-binding portion of said antibody, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in a variable domain selected from the group consisting of:

(a) the variable domain of the light chain of antibody 2.13.2;

and

(b) the variable domain of a light chain comprising the amino acid sequence in SEQ ID NO: 6;

~~_____ (c) the variable domain of the heavy chain of antibody 2.13.2;~~

~~_____ (d) the variable domain of a heavy chain comprising the amino acid sequence in SEQ ID NO: 8; and~~

~~_____ (e) the variable domain of a light chain comprising SEQ ID NO: 6 and the variable domain of a heavy chain comprising SEQ ID NO: 8.~~

35. (Currently amended) The ~~human~~ monoclonal-antibody or antigen-binding portion according to claim 34, further comprising the amino acid sequences of the heavy chain CDRs of antibody 2.13.2 and ~~light chain CDRs of antibody 2.13.2.~~

36. (Currently amended) A monoclonal antibody or an antigen binding portion thereof that specifically binds ~~human~~ insulin-like growth factor I receptor (IGF-IR), wherein said antibody comprises a ~~variable domain of a κ light chain, and wherein~~

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~~said variable domain of a κ light chain~~ comprises the amino acid sequence in SEQ ID NO: 6.

37. (Currently amended) A monoclonal antibody or an antigen-binding portion thereof that specifically binds ~~human~~ insulin like growth factor I receptor (IGF-IR), wherein said antibody comprises ~~a variable domain of a heavy chain, and wherein said variable domain of a heavy chain~~ comprises the amino acid sequence in SEQ ID NO: 8.

38. (Currently amended) The monoclonal antibody or antigen-binding portion according to claim 37, wherein said antibody further comprises ~~a variable domain of a light chain, and wherein said variable domain of a light chain~~ comprises the amino acid sequence in SEQ ID NO: 6.

39. (Currently amended) A monoclonal antibody that specifically binds ~~human~~ insulin-like growth factor I receptor (IGF-IR), wherein said antibody comprises the amino acid sequence of the heavy chain sequence within SEQ ID NO: 45, without the signal sequence, and the amino acid sequence of the light chain sequence within SEQ ID NO: 47, without the signal sequence.

40. (Currently amended) A monoclonal antibody or an antigen-binding portion thereof that specifically binds ~~human~~ IGF-IR, comprising ~~heavy chain CDR1, CDR2 and CDR3 regions, said CDR regions~~ comprising the CDR1, CDR2 and CDR3 amino acid sequences, respectively, in SEQ ID NO:45.

41. (Currently amended) The monoclonal antibody or antigen-binding portion according to claim 40, ~~wherein said heavy chain~~ further comprises comprising the framework amino acid sequences in SEQ ID NO: 45.

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42. (Currently amended) A monoclonal antibody that specifically binds ~~human~~ IGF-IR comprising the amino acid sequence of SEQ ID NO: 45, without the signal sequence, or an antigen-binding portion of said antibody.

43. (Currently amended) A monoclonal antibody or an antigen binding portion thereof that specifically binds ~~human~~ IGF-IR, comprising ~~light chain CDR1, CDR2 and CDR3 regions, said CDR regions comprising~~ the CDR1, CDR2 and CDR3 amino acid sequences, ~~respectively,~~ in SEQ ID NO: 47.

44. (Currently amended) The monoclonal antibody or antigen-binding portion according to claim 43, ~~wherein said light chain further comprises~~ comprising the framework amino acid sequences in SEQ ID NO: 47.

45. (Currently amended) A monoclonal antibody that specifically binds ~~human~~ IGF-IR comprising the amino acid sequence in SEQ ID NO: 47, without the signal sequence, or an antigen-binding portion of said antibody.

46. (Currently amended) A monoclonal antibody that specifically binds ~~human~~ insulin-like growth factor I receptor (IGF-IR) wherein the heavy chain amino acid sequence is SEQ ID NO: 45, without the signal sequence, and the light chain amino acid sequence is SEQ ID NO: 47, without the signal sequence.

47. (Previously presented) A hybridoma cell line having American Type Culture Collection (ATCC) accession number PTA-2788.

48. (Currently amended) A monoclonal antibody or an antigen-binding portion thereof, that specifically binds ~~human~~ IGF-IR, comprising the heavy chain variable domain and the light chain variable domain of the antibody produced by the hybridoma cell line of claim 47.

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49. (Previously presented) The monoclonal antibody produced by the hybridoma cell line of claim 47.

50. (Currently amended) A monoclonal antibody that specifically binds ~~human~~ IGF-IR comprising the heavy chain amino acid sequence and the light chain amino acid sequence of the antibody produced by the hybridoma cell line having ATCC accession number PTA-2788.

51. (Currently amended) A monoclonal antibody that specifically binds ~~human~~ IGF-IR comprising the amino acid sequence of the heavy chain and the amino acid sequence of the light chain of antibody 2.13.2.

52. (Previously presented) The monoclonal antibody according to claim 51, wherein the antibody is monoclonal antibody 2.13.2.

53. (Cancelled)

54. (Currently amended) A monoclonal antibody or antigen-binding portion thereof that specifically binds ~~human~~ IGF-IR, comprising a heavy chain amino acid sequence that utilizes ~~the~~ human V_H3-23 gene.

55. (Cancelled)

56. (Currently amended) A monoclonal antibody or antigen-binding portion thereof that specifically binds ~~human~~ IGF-IR, comprising a light chain amino acid sequence that utilizes the human V_K A30 gene.

57. (Currently amended) The ~~human~~ monoclonal antibody or antigen-binding portion according to claim 34, wherein said antibody is selected from the group consisting of: an immunoglobulin G (IgG), an IgM, an IgE, an IgA or an IgD molecule, a single chain antibody or a bispecific antibody.

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58. (Previously presented) The antigen-binding portion according to claim 34, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

59. (Previously presented) The antigen-binding portion according to claim 35, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

60. (Previously presented) The antigen-binding portion according to claim 36, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

61. (Previously presented) The antigen-binding portion according to claim 37, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

62. (Previously presented) The antigen-binding portion according to claim 38, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

63. (Previously presented) The antigen-binding portion according to claim 40, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

64. (Previously presented) The antigen-binding portion according to claim 41, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

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65. (Previously presented) The antigen-binding portion according to claim 42, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

66. (Previously presented) The antigen-binding portion according to claim 43, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

67. (Previously presented) The antigen-binding portion according to claim 44, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

68. (Previously presented) The antigen-binding portion according to claim 45, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

69. (Previously presented) The antigen-binding portion according to claim 48, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

70. (Previously presented) The antigen-binding portion according to claim 54, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

71. (Previously presented) The antigen-binding portion according to claim 56, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

72. (Previously presented) The antigen-binding portion according to claim 57, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

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73. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 34 and a pharmaceutically acceptable carrier.

74. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 35 and a pharmaceutically acceptable carrier.

75. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 36 and a pharmaceutically acceptable carrier.

76. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 37 and a pharmaceutically acceptable carrier.

77. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 38 and a pharmaceutically acceptable carrier.

78. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 40 and a pharmaceutically acceptable carrier.

79. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 41 and a pharmaceutically acceptable carrier.

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80. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 42 and a pharmaceutically acceptable carrier.

81. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 43 and a pharmaceutically acceptable carrier.

82. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 44 and a pharmaceutically acceptable carrier.

83. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 45 and a pharmaceutically acceptable carrier.

84. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 48 and a pharmaceutically acceptable carrier.

85. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 54 and a pharmaceutically acceptable carrier.

86. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 56 and a pharmaceutically acceptable carrier.

87. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 57 and a pharmaceutically acceptable carrier.

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88. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 39 and a pharmaceutically acceptable carrier.

89. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 46 and a pharmaceutically acceptable carrier.

90. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 49 and a pharmaceutically acceptable carrier.

91. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 50 and a pharmaceutically acceptable carrier.

92. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 51 and a pharmaceutically acceptable carrier.

93. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 52 and a pharmaceutically acceptable carrier.

94. (Cancelled)

95. (Previously presented) A pharmaceutical composition comprising the monoclonal antibody according to claim 54 and a pharmaceutically acceptable carrier.

96. (Cancelled)

97. (Previously presented) The pharmaceutical composition according to claim 73, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

98. (Previously presented) The pharmaceutical composition according to claim 74, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

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99. (Previously presented) The pharmaceutical composition according to claim 75, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

100. (Previously presented) The pharmaceutical composition according to claim 76, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

101. (Previously presented) The pharmaceutical composition according to claim 77, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

102. (Previously presented) The pharmaceutical composition according to claim 78, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

103. (Previously presented) The pharmaceutical composition according to claim 79, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

104. (Previously presented) The pharmaceutical composition according to claim 80, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

105. (Previously presented) The pharmaceutical composition according to claim 81, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

106. (Previously presented) The pharmaceutical composition according to claim 82, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

107. (Previously presented) The pharmaceutical composition according to claim 83, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

108. (Previously presented) The pharmaceutical composition according to claim 84, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

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109. (Previously presented) The pharmaceutical composition according to claim 85, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

110. (Previously presented) The pharmaceutical composition according to claim 86, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

111. (Previously presented) The pharmaceutical composition according to claim 87, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

112. (Previously presented) The pharmaceutical composition according to claim 88, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

113. (Previously presented) The pharmaceutical composition according to claim 89, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

114. (Previously presented) The pharmaceutical composition according to claim 90, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

115. (Previously presented) The pharmaceutical composition according to claim 91, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

116. (Previously presented) The pharmaceutical composition according to claim 92, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

117. (Previously presented) The pharmaceutical composition according to claim 93, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

118. (Cancelled)

119. (Previously presented) The pharmaceutical composition according to claim 95, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

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120. (Previously presented) An isolated cell line that produces the antibody according to claim 34.

121. (Previously presented) The cell line according to claim 120 that produces antibody 2.13.2, or an antibody comprising the amino acid sequences of antibody 2.13.2.

122. (Currently amended) A method for decreasing IGF-IR activation in a subject in need thereof comprising the step of administering to the subject an anti-IGF-IR antibody or ~~antigen-binding portion~~ according to claim 3934.

123. (Currently amended) A method for increasing IGF-IR associated tyrosine phosphorylation in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody or antigen-binding portion according to claim 3934.

124. (Currently amended) A method for decreasing IGF-IR signaling in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody or ~~antigen-binding portion~~ according to claim 3934.

125. (Currently amended) A method for decreasing IGF-IR binding to IGF-I or IGF-II in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody or ~~antigen-binding portion~~ according to claim 3934.

126. (Currently amended) A method for decreasing the level of IGF-IR in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody or antigen-binding portion according to claim 3934.

127. (Currently amended) A method for inhibiting tumor growth in a subject in need thereof wherein said subject overexpresses IGF-I or IGF-IR, comprising

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the step of administering to the subject an anti-IGF-IR antibody or antigen-binding portion according to claim 39~~34~~.

128. (Previously presented) The method according to claim 127, wherein the tumor is a colorectal tumor.

129. (Previously presented) The method according to claim 127, wherein the tumor is a breast cancer tumor.

130. (Previously presented) The method according to claim 127, wherein the tumor is an epidermoid carcinoma cell tumor.

131. (Previously presented) The method according to claim 26, wherein the anti-neoplastic agent is adriamycin.

132. (Currently amended) A method of detecting the presence or location of an IGF-IR-expressing tumor in a subject in need thereof, comprising the steps of:

(a) administering the antibody according to any one of claims 39, ~~or 46~~ or 51; and

(b) detecting binding of said antibody, ~~determining the expression of IGF-IR in the subject by localizing where the antibody has bound; and~~

(c) ~~diagnosing the presence or location of the tumor wherein said binding indicates the presence or [a] location of the tumor.~~

133. (Currently amended) A method of treating cancer in a human patient wherein said patient overexpresses IGF-I or IGF-IR, comprising the step of administering to the human patient an amount of the antibody according to claim 39 or 46 effective to treat said cancer.

134. (Currently amended) A method of treating a patient in need thereof with the antibody according to claim 39, ~~or 46~~ or 51, wherein said patient overexpresses

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IGF-I or IGF-IR, comprising the step of administering to the patient an effective amount of the antibody.

135. (Currently amended) The method according to either of claims 133 or 134, further comprising the step of administering an anti-neoplastic, anti-tumor, anti-angiogenic or chemotherapeutic agent.

136. (Previously presented) A method for decreasing IGF-IR activation in a subject in need thereof comprising the step of administering to the subject an anti-IGF-IR antibody according to claim 39 or 46.

137. (Previously presented) A method for increasing IGF-IR associated tyrosine phosphorylation in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody according to claim 39 or 46.

138. (Previously presented) A method for decreasing IGF-IR signaling in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody according to claim 39 or 46.

139. (Previously presented) A method for decreasing IGF-IR binding to IGF-I or IGF-II in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody according to claim 39 or 46.

140. (Previously presented) A method for decreasing the level of IGF-IR in a subject in need thereof, comprising the step of administering to the subject an anti-IGF-IR antibody according to claim 39 or 46.

141. (Currently amended) A method for inhibiting tumor growth in a subject in need thereof wherein said subject overexpresses IGF-I or IGF-IR, comprising the step of administering to the subject an anti-IGF-IR antibody according to claim 39 or 46.

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142. (Previously presented) The method according to claim 141, wherein the tumor is a colorectal tumor.

143. (Previously presented) The method according to claim 141, wherein the tumor is a breast cancer tumor.

144. (Previously presented) The method according to claim 141, wherein the tumor is an epidermoid carcinoma cell tumor.

145. (Previously presented) The method according to claim 135, wherein the anti-neoplastic agent is adriamycin.

146. (Cancelled)

147. (Cancelled)

148. (Cancelled)

149. (Cancelled)

150. (Cancelled)

151. (New) A monoclonal antibody that specifically binds insulin-like growth factor I receptor (IGF-IR) or an antigen-binding portion of said antibody, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in a heavy chain variable domain selected from the group consisting of:

(a) the variable domain of the heavy chain of antibody 2.13.2;

and

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(b) the variable domain of a heavy chain comprising the amino acid sequence in SEQ ID NO: 8.

152. (New) The monoclonal antibody or antigen-binding portion according to claim 151, wherein said antibody is selected from the group consisting of: an immunoglobulin G (IgG), an IgM, an IgE, an IgA or an IgD molecule, a single chain antibody or a bispecific antibody.

153. (New) The antigen-binding portion according to claim 151, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

154. (New) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 151 and a pharmaceutically acceptable carrier.

155. (New) The pharmaceutical composition according to claim 151, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

156. (New) An isolated cell line that produces the antibody according to claim 151.

157. (New) The monoclonal antibody or antigen-binding portion thereof according to claim 54, wherein the heavy chain amino acid sequence further utilizes a human D6-19 gene and a human JH6 gene.

158. (New) The monoclonal antibody or antigen-binding portion according to claim 56, wherein the light chain amino acid sequence further utilizes a human Jκ1 gene.

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159. (New) A method of detecting the presence or location of an IGF-IR expressing tumor in a subject, comprising the steps of:

- a) administering the antibody according to claim 56 to the subject; and
- b) detecting binding of said antibody, wherein said binding indicates the presence or location of the tumor.

160. (New) A monoclonal antibody that specifically binds insulin-like growth factor I receptor (IGF-IR) or an antigen-binding portion of said antibody, wherein the antibody or portion comprises the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the variable domain of a light chain comprising SEQ ID NO: 6 and the amino acid sequences of the CDR1, CDR2 and CDR3 regions found in the variable domain of a heavy chain comprising SEQ ID NO: 8.

161. (New) The monoclonal antibody or antigen-binding portion according to claim 160, wherein said antibody is selected from the group consisting of: an immunoglobulin G (IgG), an IgM, an IgE, an IgA or an IgD molecule, a single chain antibody or a bispecific antibody.

162. (New) The antigen-binding portion according to claim 160, wherein said portion is selected from the group consisting of: a Fab fragment, an F(ab')₂ fragment and an Fv fragment.

163. (New) A pharmaceutical composition comprising the monoclonal antibody or antigen-binding portion according to claim 160 and a pharmaceutically acceptable carrier.

164. (New) The pharmaceutical composition according to claim 160, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

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165. (New) An isolated cell line that produces the antibody according to claim 160.

166. (New) The method according to claim 24, further comprising the step of administering at least one additional chemotherapeutic agent.

167. (New) The method according to claim 24, wherein said method further comprises radiotherapy.

168. (New) The method according to claim 133, further comprising the step of administering at least one additional chemotherapeutic agent.

169. (New) The method according to claim 133, wherein said method further comprises radiotherapy.